BIOGRAPHICAL SKETCH

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NAME: Wu, Hao

POSITION TITLE: Asa and Patricia Springer Professor of Biological Chemistry and Molecular Pharmacology

eRA COMMONS USER NAME (credential, e.g., agency login): haowuwmc

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking University, Beijing, China	B. Sc. Equiv.	05/1985	Biology
Peking Union Medical College, Beijing, China	MD candidate	06/1988	Medicine
Purdue University, West Lafayette, Indiana	Ph.D.	03/1992	Biochemistry
Columbia University, New York, New York	Postdoc	01/1997	Biochemistry

A. Personal Statement

Since starting her own laboratory in 1997, the PI has focused on structural immunology, in particular, the structural basis of intracellular signal transduction in the mammalian immune system. Her contributions began in the TNF receptor pathway, which is inappropriately activated in autoimmune states such as rheumatoid arthritis (RA) and Crohn's disease. Blockade of TNF functions with drugs like Humira, correspondingly has had major therapeutic implications. The PI's laboratory has elucidated precise structural bases for how TNF signaling occurs and, thereby, provided a rational basis for understanding the most effective therapies for these conditions. The PI also elucidated the structural basis for signal transduction of the pro-inflammatory interleukin-1 receptor (IL-1R) family (such as receptors for IL-1, IL-18 and IL-33) and the Toll-like receptor (TLR) family, which share a set of overlapping cytoplasmic signaling proteins with the TNF receptor family. Most recently, the PI's laboratory performed structural studies on inflammasomes, which are cytosolic complexes for caspase-1 activation. In all areas, a unifying theme - revealed in substantial part by the PI's contribution - has been the identification and functional characterization of large oligomeric protein complexes that mediate these signaling cascades.

The PI is experienced in many aspects of structural biology, including protein crystallography, biochemistry, and biophysics. Her current work also extends to electron microscopy, cellular imaging and structure-based drug design.

B. Positions and Honors

1997-2001 Assistant Professor of Biochemistry, Weill Medical College of Cornell University
2001-2003 Associate Professor of Biochemistry, Weill Medical College of Cornell University
2003-2012 Professor of Biochemistry, Weill Medical College of Cornell University
2012- Asa and Patricia Springer Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, and the Program in Cellular and Molecular Medicine, Boston Children's Hospital

International Math Olympiad, 1981
Highest entering grades to Peking Union Medical College in National College Entrance Examination, 1982
Top in class and outstanding academic achievement, Peking Union Medical College, 1982-1988
Member of Gamma Sigma Delta, 1989
Howard Hughes Medical Institute Predoctoral Fellowship, 1989-1992
Aaron Diamond Foundation Postdoctoral Fellowship, 1993-1996
Pew Scholar Award, 2000-2004

Rita Allen Scholar Award, 2002-2004
Margaret Dayhoff Memorial Award, Biophysical Society, 2003
Mayor's Award for Excellence in Science and Technology, 2003
Editorial Board, Cancer Cell, 2012-
Editorial Board, F1000 Research, 2012-
NIH Merit Award, 2012-2022
Elected AAAS Fellow, 2013
Purdue University Distinguished Science Alumni Award, 2013
Elected Member of the National Academy of Sciences, 2015

C. Contributions to Science (in approximate chronological order)

Elucidation of the specificity and oligomerization mechanism of TNF receptor associated factors (TRAFs, 1/2/3/5 and 6), which are the major signaling proteins for TNF receptor family-, IL-1R family-, and TLR-family-induced NF-κB activation. When the PI started working on TRAFs, no structural information was available. The PI identified consensus motifs for different TRAFs using structural studies, which became widely used tools for biologists. The PI's work also led to understanding the ubiquitin ligase activity of TRAF6 and its dependence on dimerization and higher-order oligomerization.

Y. C. Park, V. Burkitt, A. R. Villa, L. Tong and H. Wu (1999). Structural basis for self-association and receptor recognition of human TRAF2. ***Nature*** 398: 533-8
Y. C. Park, H. Ye, C. Hsia, D. Segal, R. L. Rich, H. C. Liou, D. G. Myszka and H. Wu (2000). A novel mechanism of TRAF signaling revealed by structural and functional analyses of the TRADD-TRAF2 interaction. ***Cell*** 101: 777-87
H. Ye, J. R. Arron, B. Lamothe, M. Cirilli, T. Kobayashi, N. K. Shevde, D. Segal, O. K. Dzivenu, M. Vologodskaia, M. Yim, K. Du, S. Singh, J. W. Pike, B. G. Darnay, Y. Choi and H. Wu (2002). Distinct molecular mechanism for initiating TRAF6 signaling. ***Nature*** 418: 443-7
Q. Yin, S. C. Lin, B. Lamothe, M. Lu, Y. C. Lo, G. Hura, L. Zheng, R. Rich, A. D. Campos, D. G. Myszka, M. J. Lenardo, B. G. Darnay and H. Wu (2009). E2 interaction and dimerization in the crystal structure of TRAF6. ***Nat Struct Mol Biol*** 16: 658-66 PMC2834951

Elucidation of activation and inhibitory mechanisms of caspases and kinases. These enzymes are critically important for apoptotic and inflammatory signaling and were often difficult to obtain structures of. The understanding on their regulatory mechanisms revealed by work from the PI's lab is now being used for discovery of small molecule inhibitors for potential disease therapy.

Y. Huang, Y. C. Park, R. L. Rich, D. Segal, D. G. Myszka and H. Wu (2001). Structural basis of caspase inhibition by XIAP: differential roles of the linker versus the BIR domain. ***Cell*** 104: 781-90
G. Xu, M. Cirilli, Y. Huang, R. L. Rich, D. G. Myszka and H. Wu (2001). Covalent inhibition revealed by the crystal structure of the caspase-8/p35 complex. ***Nature*** 410: 494-7
G. Xu, Y. C. Lo, Q. Li, G. Napolitano, X. Wu, X. Jiang, M. Dreano, M. Karin and H. Wu (2011). Crystal structure of inhibitor of κB kinase β (IKKβ). ***Nature*** 472: 325-30 PMC3081413
Ferrao R, Zhou H, Shan Y, Liu Q, Li Q, Shaw DE, Li X and Wu H (2014). IRAK4 Dimerization and Trans-autophosphorylation are Induced by Myddosome Assembly. ***Mol Cell*** 55:891-903 PMC4169746

Identification of functional amyloid assembly in TNF-induced programmed necrosis. The PI's lab showed the surprising finding that the RHIM domain-containing proteins assemble into amyloid filaments to activate kinases and to induce cell death. These studies opened up new directions of research.

J. Li, T. McQuade, A. B. Siemer, J. Napetschnig, K. Moriwaki, Y.-S. Hsiao, E. Damko, D. Moquin, T. Walz, A. McDermott, F. K.-M. Chan, and H. Wu (2012). The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. ***Cell*** 150: 339-50 PMC3664196

Discovery of helical signaling complexes including helical filaments formed by the death domain superfamily proteins. These protein domains were known for their tendencies to aggregate. The PI's lab elucidated that they assemble into either relatively defined helical complexes or helical filaments. These structures help to establish a new paradigm of signal transduction in innate immunity.

H. H. Park, E. Logette, S. Rauser, S. Cuenin, T. Walz, J. Tschopp and H. Wu (2007). Death domain assembly mechanism revealed by crystal structure of the oligomeric PIDDosome core complex. ***Cell*** 128: 533–46
S. C. Lin, Y. C. Lo and H. Wu (2010). Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signaling. ***Nature*** 465: 885-90 PMC2888693
Q. Qiao, C. Yang, C. Zheng, L. Fontan, L. David, X. Yu, C. Bracken, M. Rosen, A. Melnick, E. H. Egelman and H. Wu (2013). Structural Architecture of the CARMA1/Bcl10/MALT1 Signalosome: Nucleation-Induced Filamentous Assembly. ***Mol Cell*** 51: 766-79 PMC3929958
A. Lu, V. G. Magupalli, J. Ruan, Q. Yin, M. K. Atianand, M. R. Vos, G. F. Schröder, K. A. Fitzgerald, H. Wu* and E. H. Egelman (2014). Unified Polymerization Mechanism for the Assembly of ASC-Dependent Inflammasomes. ***Cell*** 156: 1193-206 PMC4000066 *Sole corresponding author

Discovery of the overarching principle of higher order assemblies and their important properties in signaling.

H. Wu (2013). Higher-order assemblies in a new paradigm of signal transduction. ***Cell*** 153: 287-92 PMC3687143
Kagan JC, Magupalli V, Wu H. (2014). Supramolecular Organizing Centres (SMOCs): Site-Specific Higher Order Signalling Complexes that Control Innate Immunity. ***Nature Rev Immunol***. 14:821-6 PMC4373346

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/hao.wu.1/bibliograpahy/40701424/public/?sort=date&direction=ascending

D. Research Support

Ongoing Support

The Michael J. Fox Foundation 2/26/16-2/25/17 Role: PI
Biochemical analysis and structural determination of LRRK2 with kinase inhibitors
The major goal of this project is to determine the crystal structure of LRRK2 in complex with kinase inhibitors.

Janssen Biotech Inc. 12/17/14-12/17/17 Role: PI
Structural biology of MALT-1 small molecule inhibitors
The major goal of this collaborative project is to develop potent chemical compounds that are suitable for clinical advancement in patients with lymphomas.

1DP1 HD087988-01 (Wu, H) 09/30/15-07/31/20 NIH/NICHD (Role: PI)
SMOCs: Novel Signal Transduction Complexes as New Targets for Drug Discovery
The major goal of this project is to investigate signal transduction in order to guide the development of new models for targeted drug discovery.

5R01 AI050872-13 (Wu, H) 01/01/02-03/31/17 NIH/NIAID (Role: PI)
Structural & Functional Studies of TLR/IL-1R Signaling
The major goal of this project is to assemble the membrane-proximal signaling complexes and to elucidate the molecular basis of this signal transduction.

5R01 AI045937-12 (Wu, H) 07/01/99-06/30/17 NIH/NIAID (Role: PI)
Structural and functional elucidation of the necrosome in innate immune signaling
The major goal of this project is to elucidate the molecular basis of TNF-induced necrosis.

5R01 CA154228-03 (Cesarman, E) 03/15/11-01/31/16 NIH/NCI (Role: Co-Investigator)
Targeting vFLIP for the treatment of KSHV-associated Malignancies
The major goal of this project is to identify small molecule inhibitors of vFLIP.

1R01 CA182736-01 (Gray, N) 09/26/13-08/31/18 NIH/NCI (Role: Co-Investigator)
MALT1 inhibitors for the treatment of chemo-resistant ABC-DLBCL
The major goal of this project is to optimize MALT1 inhibitors using structure-based chemical approaches

Completed Support:

5R01 AI089882-05 (Wu, Hao) 05/01/10 – 04/30/15 NIH/NIAID (Role: PI)
Molecular Elucidation of the CBM complex in NF-kappaB Activation by Antigen Receptors
The major goal of the project is to elucidate the molecular basis of CBM signaling in TCR and BCR activation

LLS (Melnick, A) 10/01/11 – 09/30/14 Role: Co-Investigator
Leukemia & Lymphoma Society
Therapeutic targeting of the MALT1 protein for chemoresistant lymphomas
The major goal of this project is to therapeutically target MALT1.

5R01 AI079260-06 (Wu, Hao) 06/25/09-06/30/14 NIH/NIAID (Role: PI)
Structural and Functional Studies of the IkappaB Kinase (IKK) Complex
The major goal of the project is to enhance the understanding of kinase activation and inhibition in general.

5R21 AI096554-02 (Menon, AK) 06/01/11 – 05/31/13 NIH/NIAID (Role: Co-Investigator)
Structural Analysis of the GPI Transamidase ComplexThe main objective is to analyze the GPI transamidase complex from a structure-function perspective.
The complex will be isolated from yeast and studied by electron microscopy; subunits, sub-complex and eventually the entire transmembrane complex will be characterized by X-ray crystallography.

7R01 AI076927-05 (Wu, Hao) 07/01/08-06/30/13 NIH/NIAID (Role: PI)
Structural and Functional Studies of the Caspase Activating Complex Piddosome
The major goal of the project is to elucidate the molecular basis of PIDDosome formation.

Prostate Cancer Foundation (Rubin,M) 8/01/11 – 7/31/13 Role: Co-Investigator
Recurrent SPOP Mutations in Prostate Cancer: Characterization of a Potentially Targetable Subclass
The major goal of this project is to study the frequency and functional significance and substrates of SPOP PCA, pursuing small molecular inhibitors for altered pathways leading to preclinical studies